REMARKS

Claims 32-42 are pending in this application. No claims have been amended in this response.

Applicants note with appreciation the acceptance of the RCE filed June 10, 2005 and that in response to the amendments accompanying the RCE, the Office has withdrawn "all rejections of record" in favor of newly presented claim rejections (emphasis original, see Office Action, p. 2.)

CLAIM REJECTIONS – 35 U.S.C. § 103

Claims 32-42 stand rejected for alleged obviousness over Raveendranath (Raveendranath '293) in view of Sawicka. Similarly, claims 32-42 stand rejected for alleged obviousness over Miller (Miller '183) in view of Sawicka.

Claims 32-42 are rejected under 35 U.S.C. § 103(a) for alleged obviousness based on Raveendranath, et. al., WO9919293 (hereinafter "Raveendranath '293") and Sawicka, Pharmazie, 1991, vol. 46, p. 519-521 (hereinafter "Sawicka"). Applicants respectfully request reconsideration of the rejection, as the cited art, either alone or in combination, neither discloses nor suggests the claimed pharmaceutical compositions.

Claims 32-42 are rejected under 35 U.S.C. § 103(a) for alleged obviousness based on Miller, et. al., EP802183 (hereinafter "Miller '183") and Sawicka. Applicants respectfully request reconsideration of the rejection, as the cited art, either alone or in combination, neither discloses nor suggests the claimed pharmaceutical compositions.

In particular, the Office Action asserts Raveendranath '293 discloses a pharmaceutical composition comprising 2-(4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperdin-1-yl-ethoxy)-benzyl]-1H-

indol-5-ol (Office Action, p. 3) and that Miller '183 discloses a pharmaceutical composition comprising 2-(4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperdin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol or 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol. (Office Action, p. 6). It further alleges that Miller '183 teaches said composition further comprising a filler, disintegrant, wetting agent, lubricant, and a glidant (Office Action, p.7-8). The rejections are nearly identical, and even quote nearly (if not entirely) identical passages from the references. The Action admits that neither reference teaches use of an antioxidant in this pharmaceutical composition and does not specify ranges for each of the components. The Action goes on to conclude that the inclusion of an antioxidant, not disclosed by either Raveendranath '293 or Miller '183, was obvious based on Sawicka. It further concludes that one of ordinary skill in the art would have been motivated to determine the specific ranges of each of the various components of the claimed composition because the excipients are known fillers, known disintegrants, etc.

The combination of references does not teach or suggest every element of the claims

Applicants respectfully submit neither Raveendranath '293 nor Miller '183 discloses or suggests the wetting agent and glidant elements required generically by Claims 35-42 nor does either reference recognize the specific wetting agents and glidants, as such, set forth in claims 32-34.

Contrary to the Office Action's assertion, Raveendranath '293 and Miller '183 do not disclose the use of either a wetting agent or a glidant in the disclosed pharmaceutical composition containing the indol-5-ol compounds. To support its interpretation, the Office cites

a paragraph from Raveendranath '293 and Miller '183 concerning oral formulations. The following portion of Miller '183 is representative of the quoted paragraphs:

> Oral formulations containing the active compounds of this invention may comprise any **conventionally** used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s).

(emphasis added in the Office Action, p. 7). This paragraph does not teach the use of glidants or wetting agents in the formulation. The references contain no explicit or implicit reference to either a wetting agent or to a glidant. Instead, they refers only to fillers, diluents, binding agents, lubricants, disintegrants, and suspending or stabilizing agents. These enumerated exicipients function differently than either wetting agents or glidants. For example, fillers and diluents are used to form tablets or capsules of a desired size. Binding agents can be used to impart mechanical strength to a composition. Lubricants can insure powder does not adhere to the processing equipment. Disintegrants encourage break up of the tablet in water and can be hydrophilic materials without any surface tension lowering property. Suspending or stabilizing agents can stabilize granule suspensions during processing.

By contrast, wetting agents serve a much different purpose from any of the excipients enumerated in quoted paragraph. For example, wetting agents allow spreading and penetration of water into dry granules by lowering the surface tension of water, which can be helpful during processing. Glidants improve flowability of powder formulation during processing. Thus, it is apparent that wetting agents and glidants do not have the same function nor the same mechanism as fillers, diluents, binding agents, lubricants, disintegrants, or suspending or stabilizing agents. Hence, neither Raveendranath '293 nor Miller '183 teaches or suggests a pharmaceutical composition containing a wetting agent and a glidant, as required by each of the pending claims. For this reason alone, the rejections under 35 U.S.C. § 103 should be withdrawn.

Furthermore, the quoted section of Miller also does not suggest the use of a wetting agent or a glidant. The "laundry list" of compounds at the end of the Office Action's selected quotation from Miller includes sodium lauryl sulfate, which the present application identifies as a wetting agent in dependent claim 42. However, Miller's recitation of sodium lauryl sulfate does not suggest the use of sodium lauryl sulfate as a wetting agent. On the contrary, Miller's "laundry list" of compounds is explicitly identified as belonging to a discrete class of excipients which includes only "diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents." (Office Action, p. 7; Miller, p. 13). Hence, Miller clearly does not suggest that sodium lauryl sulfate is being used as a wetting agent. Rather, it suggests its use only as a diluent, binding agent, lubricant, disintegrant, suspending or stabilizing agent. The present application notes, on page 6, that " Some components may have multiple functions in the formulations of this invention, acting e.g. as both a filler and a disintegrant, such a component may be referred to as a filler disintegrant and its function in a specific formulation may be singular even though

its properties may allow multiple functionality." Thus, Applicants recognize a single agent may span multiple excipient categories. Neither Raveendranath '293 nor Miller '183 recognize this or even that any of its recited excipients can function as a wetting agent or a glidant. One of ordinary skill in the art, reading Raveendranath '293 or Miller '183, would not have been motivated to include a wetting agent or glidant in the present formulation.

Sawicka was combined, separately, with both Raveendranath '293 and Miller '183. Sawicka, however, does not discuss the use of wetting agents or glidants. Sawicka is directed to and cited for its disclosure of an antioxidant. The combination with Sawicka does not overcome the deficiencies of either Raveendranath '293 or Miller '183 with respect to a wetting agent or a glidant. Accordingly, the claimed invention, requiring each of these elements, is not obvious over the combinations. For this reason alone, the rejections under 35 U.S.C. § 103 should be withdrawn.

The determination of the required excipient classes is not obvious nor is the optimization of ranges thereof

The Office Action also states that one of ordinary skill in the art would have been motivated to determine the specific ranges for each of the excipients because a composition was known which comprised "the instant compound and a pharmaceutical carrier or excipient system....comprising a filler and disintegrant components, a wetting agent, a lubricant, and a glidant." (Office Action, p. 8). Applicants respectfully disagree.

As part of its argument, the Office states that according to the references, "the determination and the optimization of amounts of known excipients such as a known filler, known disintegrant components, a known wetting agent, a known lubricant, and a known glidant

in a pharmaceutical composition are considered **conventional** to an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art." (emphasis original) Applicants respectfully submit that the reference to conventional made in both Raveendranath '293 and Miller '183 is made to "**conventionally** used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions." (Office Action quoting Raveendranath '293 and Miller '183, emphasis in Office Action). The oral forms of a tablet, capsule, etc. are referred to as conventional. Neither reference contains reference to a the inclusion of any classes of excipients, such as wetting agent, lubricant, glidant, etc. or, as the Office admits, any range of excipients, conventional or otherwise. Thus, any discussion of conventional in the references refers to the form of the dosage, not its content either by constituent or amount. The references, accordingly, do not and cannot teach Applicants' presently claimed formulation is "conventional."

In addition, the Action notes that the "determination and optimization" of the amounts of the excipients would be well known in the art. The Action cites *In re Boesch*, 205 USPQ 215 (CCPA 1980) in support of this position. Applicants note, however, that MPEP § 2144.05 II B. (which cites *In re Boesch*) makes it clear that a "particular parameter must first be recognized as a result-effective variable, i.e. a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." (citing *In re Antonie*, 195 U.S.P.Q. 6 (CCPA 1977).)

The Court in *In re Antonie*, 195 U.S.P.Q. 6 (CCPA 1977). stated:

> The PTO and the minority appear to argue that it would always be obvious for one of ordinary skill in the art to try varying every parameter of a system in order to optimize the effectiveness of the system.... As we have said many times, obvious to try is not the standard of 35 U.S.C. §103. (Citing *In re Tomlinson*, 53 C.C.P.A. 1421, 363 F.2d 928, 150 U.S.P.Q. 623 (1966)).

The court reiterated the baseline rule that it is not inventive to discover optimum or workable ranges where the general conditions of a claim are disclosed in the prior art. However, the Court concluded:

> We have found exceptions to this rule in cases where the results of optimizing a variable, which was known to be result effective, were unexpectedly good. *In re Weymouth*, 499 F.2d 1273, 182 U.S.P.Q. 290 (CCPA 1974); *In re Saether*, *supra*. **This case, in which the parameter optimized was not recognized to be a result-effective variable, is another exception.** The decision of the board is reversed. (emphasis added.)

Thus, to uphold an obviousness rejection, the references must recognize that the parameter is a result-effective variable before it can be optimized through routine experimentation.

Inclusion of Wetting Agent and Glidant is not taught or suggested and optimization of ranges thereof cannot be obvious

At a minimum, because neither Raveendranath '293 nor Miller '183 suggests inclusion of either or both a wetting agent and a glidant and these excipient classes are functionally different from those classes of excipients recognized by the references, they certainly cannot recognize whether these components are result-effective. Accordingly, optimization of ranges of wetting agent and glidant is not obvious. One skilled in the art could not determine for what purpose or property the range should be optimized, even where a compound potentially useful as a wetting agent or glidant is disclosed. For example, Raveendranath '293 and Miller '183 disclose the use of sodium lauryl sulfate, but not as a glidant or wetting agent. The optimal range for sodium lauryl sulfate as a wetting agent would be different than the optimal range for sodium lauryl sulfate as one of the other excipient classes. One of ordinary skill reading Raveendranath '293 or Miller '183, therefore, could not have accurately determined the desired range for sodium

lauryl sulfate (or any other wetting agent or glidant) in the formulation. For this reason alone, the rejection should be withdrawn.

None of the claimed excipients are recognized as result-effective by the art of record, therefore, optimizing the amounts thereof is not obvious

Applicants have recognized that certain combinations of filler and disintegrant where the disintegrant comprises 4-40% of the formulation combined with a lubricant in the claimed amounts, results in a formulation having rapid dissolution properties and enhanced stability. Applicants have further recognized that such properties are maintained when a wetting agent, and glidant are added in the claimed ranges, as set forth in independent claim 35.

The cited art does not recognize the need or usefulness of either a wetting agent, or a glidant, or even absent these components, the importance of the combined filler and disintegrant, and lubricant in the claimed ranges. No factual basis has been provided by the Office to show the prior art teaches, suggests, or provides motivation for one skilled in the art to employ the claimed components for their recited purposes, much less in the claimed amounts.

Only Applicants have sought to provide a pharmaceutical composition that optimizes the stability and enhances the dissolution of poorly soluble pharmaceutical agents such as estrogenic agents. In fact, the only reference to dissolution properties in Raveendranath '293 and Miller '183 refers to "standard delay or time release formulations." In sharp contrast, Applicants' invention provides for "rapid dissolution of poorly soluble drugs" (application p. 3) rather than delayed release. The art of record simply does not teach or suggest Applicants' claimed formulation.

Applicants' claimed invention, as exemplified in claim 35 includes, each within a claimed range, a filler and disintegrant component, a wetting agent, an antioxidant, a glidant, and a lubricant, in addition to the active ingredient. With the references of record to guide them, those skilled in the art would have to experiment with a myriad of excipients, without knowing or appreciating the end goal of rapid dissolution and enhanced stability, and without realizing they were looking to include *each* of a combined filler and disintegrant component, a wetting agent, a glidant, an antioxidant, and a lubricant, as presently claimed. In this search, those skilled in the art would have to conclude their experiments showed that *each* of a filler and disintegrant component, a wetting agent, a glidant, and a lubricant are required in the formulation, all without direction from the art.

Assuming, *arguendo*, those skilled in the art decided to include *each* such component, they would then have to experiment with each to find the "optimal" ranges for each to reach the claimed invention -- all without any direction or suggestion in the art to do so, and without the goals of rapid dissolution and enhanced stability, as taught by Applicants, in mind. Those skilled in the art, absent Applicants' teachings, simply did not recognize the amounts of the filler and disintegrant component and lubricant were result-effective variables for obtaining a rapid dissolve formulation for active ingredients with poor solubility. Those of skill in the art would not merely be finding optimal ranges, since they failed to recognize the result-effective nature of any of the claimed components. Accordingly, Applicants' claims including such ranges are not obvious under 35 U.S.C. § 103.

Since the references do not teach or suggest the specific ranges for each of the excipient classes required by the claims or even the importance of including a component from each of the claimed classes of excipients, those of ordinary skill in the art could not possibly

have been motivated to determine specific ranges for any of the excipients, particularly the wetting agent or glidant, which are not disclosed by any of the cited references.

Neither Raveendranath '293 nor Miller '183 teach or suggest the claimed pharmaceutical formulation. Only Applicants teach a pharmaceutical composition including the claimed active ingredient, and the claimed filler and disintegrant component, the wetting agent, the lubricant, the antioxidant, and the glidant in the claimed ranges. It is well settled that Applicants' own teaching cannot provide the blue print for combining or modifying references, that motivation must come from the art, not from impermissible hindsight reconstruction.

Sawicka is silent with regard to glidants, and wetting agents as well as to rapid release properties. As such, the combination of Sawicka with either Raveendranath '293 or Miller '183 does not overcome the deficiencies of those references as discussed above. Accordingly, Applicants need not address whether the combination of Sawicka properly provides motivation to include the required anti-oxidant. Even if there were proper motivation to combine, the combined references still do not teach or suggest every claimed element.

Accordingly, applicants respectfully submit that all pending claims are allowable over the cited art.

DOUBLE PATENTING

The present claims stand rejected under the judicially created doctrine of non-statutory double patenting for alleged obviousness over US 6,479,535 assigned to the Assignee of the present application. Although Applicants respectfully assert that the discussion above is relevant to the '535 patent as well, upon indication of otherwise allowable claims, Applicants will file a terminal disclaimer as an administrative expedient, if required.

The Commissioner is hereby authorized to charge any fee or underpayment thereof or credit any overpayment to deposit account no. 50-1275.

Early reconsideration and allowance of all pending claims is respectfully requested. The examiner is requested to contact the undersigned attorney if an interview, telephonic or personal, would facilitate allowance of the claims.

Respectfully submitted,

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